IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Tommy Ekstrom	Art Unit	: 1617
Serial No.	: 10/665,240	Examiner	: Kendra D. Carter
Filed	: September 19, 2003	Conf. No.	: 6971
Title	: NEW USE		

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REPLY TO ACTION OF JUNE 12, 2009

Please consider the following remarks in reply to the Office action dated June 12, 2009. This Reply is being filed with a Request for Continued Examination, an Information Disclosure Statement, and a petition for extension of time.

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I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: December 11, 2009

REMARKS

Claims 13-29, 34, 36 and 42-56 remain pending and under examination in the application. No amendments are presently proposed. The claims stand rejected on grounds that are discussed below. Applicants respectfully request that the Examiner reconsider and withdraw the rejections in view of the arguments and evidence below.

Rejection for Obviousness-type Double Patenting

The Office action dated June 12, 2009 (the "Office action") provisionally rejects claims 13-15, 17, 19, 20, 22-25, 34, 36, 42, and 53 on the ground of nonstatutory double patenting over certain claims of copending application no. 09/367,950. As yet, the claims of application no. 09/367,950 have not been allowed. Applicants reiterate (and thank the Examiner for acknowledging) Applicants' stated intent to file a terminal disclaimer in one of the two applications if such is still deemed appropriate once the claims of one of the two applications are allowed.

Rejection under 35 USC § 103(a) for Obviousness over Carling

Claims 13-15, 17, 18, 20-29, 34, 36, and 42-56 were rejected as obvious over a single reference, Carling et al., WO 9311773 A1 ("Carling"). The Office action at pages 6-9 repeats the ground of rejection of these claims over Carling nearly word-for-word as stated in the preceding Office action dated September 19, 2008 (the "9/19/08 Action"). In addition, the Office action at pages 12-15 addresses Applicants' prior arguments regarding the rejection over Carling as set forth in Applicants' Reply filed March 18, 2009 (the "3/18/09 Reply")].

As the ground of rejection for obviousness as stated at pages 6-9 of the Office action is essentially identical to the ground as stated on pages 6-10 of the 9/19/08 Action, Applicants begin by reaffirming the arguments provided in the 3/18/09 Reply at pages 8-20, which fully addressed that ground of rejection. For efficiency, rather than repeat the arguments from pages 8-20 of Applicants' 3/18/09 Reply here, Applicants simply incorporate those arguments by reference into the present Reply and focus instead on addressing just a few of the points made on

pages 6-9 of the present Office action, as well as the Examiner's further comments that appear at pages 12-15 of the present Office action.

First, Applicants note the Examiner's reliance on Carling's teachings that a "suitable daily dose for budesonide is in the range of 50 to 4800 μg with a preferred dose of 100-1600 μg" and that some examples of inhalers can deliver 200 μg budesonide per actuation. This does not amount to a teaching that the doses can be delivered in up to 8 separate administrations over the course of the day, at the patient's discretion, as the Examiner apparently believes. Rather, given that Carling explicitly and repeatedly stated that the budesonide/formoterol combination is supposed to be delivered just twice per day (see page 4, lines 19-21 (" a twice daily dosing regime as a basic treatment of asthma") and page 6, lines 22-23 ("The intended dose regimen is a twice daily administration"), it is clear that Carling did NOT intend that the doses be spread out into more than two administrations over the course of the day. If the physician decides that the patient should receive a relatively high daily dose (e.g., 1600 μg per day), for example, because the patient is heavy, or suffers from a particularly severe condition, and if the available inhaler delivered just 200 μg per actuation, the physician would instruct the patient to do multiple (e.g., four) activations of the inhaler device at each of the two administration times per day (e.g., morning and evening), to provide a sufficient daily dose to help prevent asthma symptoms from developing over the long term. Physicians of ordinary skill in the art were well aware of the potential hazards of therapy with steroid drugs (even relatively safe ones like budesonide), and knew to minimize use of these drugs and put strict limits on how they are used by patients. See, for example, the budesonide product insert that is Exhibit 1 filed with Applicants' Reply dated July 27, 2007 (the "7/27/07 Reply"), which makes it clear that the patient should not alter the prescribed dosage of budesonide unless advised to do so by the physician (see, e.g., the section labeled "C" in Exhibit 1). Thus, one of ordinary skill in the art would not read Carling as promoting the idea that the budesonide/formoterol combination could be administered more than two times per day, and certainly not that the patient could decide for him or herself how many administrations to employ on any given day.

Page 12 of the Office action sets out the Examiner's summary of some of Applicants' arguments regarding Carling and then says,

> The Examiner continues to disagree for the same reasons given before and repeated below. One of ordinary skill in the art would be motivated and found it obvious to combine the method of Carling et al. and administering the method on an irregular, as-needed basis for rescue purposes, as determined by the patient in any of the circumstances detailed in claims 13, 34, 36 and 42 because Carling et al. teaches that the dosages strongly depends on the severity of disease, whether mild, moderate, or sever asthma (see pg 6, lines 27-29), and the suitable daily dosage is up to 8 inhalation (see page 7-9). (Grammatical and spelling errors in the original)

Applicants again remind the Examiner that, in view of all of the objective evidence currently of record, Carling's teaching at page 6, lines 27-29, that "the particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)" would have been read by one of ordinary skill in the art as meaning that the prescribing physician would make these determinations for a given patient, and not that the patient him/herself would do so. The Examiner has provided nothing more than her own conclusory statements as to how one of ordinary skill would interpret this passage of Carling, and certainly has not countered any of the many lines of objective evidence provided by Applicants in this regard. Applicants have shown that those of ordinary skill in the art understood at the time of the invention that inhaled budesonide should be administered no more than twice per day, and only in the precise daily doses specified by the prescribing physician (see, e.g., Exhibit 1 submitted with the 7/27/07 Reply, and the detailed explanation of this Exhibit that appears on pages 16-18 of the 7/27/07 Reply). Exhibit 1 strongly warns the patient not to inhale more doses or more often than the doctor advises (see the text labeled "B" on page 2 of Exhibit 1) and says "**The patient should not alter the prescribed dosage unless advised to do so by the physician... If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician**" (see text labeled "C" on page 3 of Exhibit 1). The Examiner has refused to grant any evidentiary weight to Exhibit 1, saying only, "The Examiner notes that the evidence provided in Exhibit 1 is not commensurate to scope with the claimed invention because the Exhibit 1 is administration of budesonide as the sole active ingredient, while the claimed invention is an admixture of budesonide and formoterol." Office action at page 13. Applicants agree that Exhibit 1 concerns administration of budesonide as the sole active ingredient, but disagree that this is an excuse to

dismiss its teachings. The Examiner has not explained why she believes a physician of ordinary skill in the art who is considering Carling's method of administering a combination of budesonide with another drug would simply ignore all prior teachings about how budesonide should be administered, including warnings that pertain to safe use of budesonide. Applicants are unaware of any case law establishing that a prior art teaching away can be dismissed as irrelevant if it does not address every limitation of the claim, and again[1] ask the Examiner to provide such case law if she intends to maintain her unusual position regarding Exhibit 1. According to the Court of Appeals of the Federal Circuit, "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006)(quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). *See* also, *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966) ("Known disadvantage in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness.") Applicants submit that Exhibit 1 would certainly have discouraged one of ordinary skill from using any budesonide-containing composition in the manner the Examiner supposes is "obvious" based on Carling, and would have led one of ordinary skill in a direction divergent from the method that is presently claimed. The Examiner has cited no evidence to the contrary. Thus, Applicants believe the teaching-away is established, and the rejection should be withdrawn on that ground alone.

Exhibit 2 filed with the 7/27/07 Reply is a product insert circa 2001 for SYMBICORT TURBUHALER®, a budesonide/formoterol inhalation powder product similar to that disclosed by Carling. Exhibit 2 shows that, even years after the present application's priority date, those of ordinary skill in the art understood that budesonide-containing compositions (including those containing formoterol as a second active ingredient) should be inhaled no more than twice per day, and the physician must dictate the dosage and whether it is given once or twice per day. See the detailed description of Exhibit 2 at page 19 of the 7/27/07 Reply.

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[1] Applicants' 3/18/09 Reply also asked the Examiner to provide a citation to such a case.

The Office action at page 14 says this of Exhibit 2:

> In regards to Exhibit 2, the statements D and E verifies the Examiner's statement that patients will take more than the current dose if needed. Although the additional doses are not recommended, it is not impossible to not take an additional administration if the patient feels the need for treatment. In an asthma attack, if a patient is faced with not breathing and taking an additional administration within the safe inhalation amounts, one would find that the patient would take an as-needed administration. Further, if the patient did not need the additional administration, the prior art clearly reads on the claimed invention. (Emphasis and informal English in the original.)

Applicants strenuously disagree with the Examiner's interpretation of Exhibit 2's statements labeled "D" and "E." Neither of these statements "verifies" the notion that "patients will take more than the current dose if needed," as the Examiner asserts. Quite to the contrary.

Sentence "D" reads: "**If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought**." Whether this means it is or isn't "impossible" to exceed the recommended twice-daily dosing regimen is not the issue, despite the Examiner's apparent belief that it is. (See the quoted text from the Office action above regarding what the Examiner says is "not impossible".) A reference doesn't have to indicate something is "impossible" in order to show that those of ordinary skill in the art would know not to do it. Plainly, those of ordinary skill in the art would know, based on sentence "D", not to take more than two administrations even if the treatment with two administrations per day was not working. Sentence "D" tells the patient to seek medical attention—i.e., to consult the physician--if the twice-daily regimen is ineffective. It does not tell the patient to take further doses of the Symbicort® combination if the patient feels it necessary. It is up to the patient's physician to decide whether the treatment is insufficient and to consider increasing the dose that is given twice daily, or perhaps trying a different drug altogether. These decisions (and certainly any decision about taking a third or further administrations in a given day) are not left to the patient. In fact, as sentence "D" explicitly states, if the patient does inadvertently exceed the prescribed dose of the Symbicort® combination on some occasion, the patient must seek medical attention. Exceeding the prescribed dosage is apparently regarded as being so potentially problematic that the doctor must be told when it occurs. This is within the "Special warnings and precautions for use" section of the Exhibit 2 product insert, further evidence that it is a

serious warning to the doctor and patient. Thus, sentence "D" demonstrates the art's understanding that the budesonide/formoterol combination should NOT be administered more than twice per day, and should NOT be administered in a dose that exceeds what the physician prescribed for the twice-per-day regimen, even if the patient finds the prescribed treatment to be ineffective.

Sentence "E" of Exhibit 2 says, "**Increasing use of rescue bronchodilators indicates a worsening of underlying condition and warrants a reassessment of the asthma therapy.**" A "rescue bronchodilator" as that term is used in Exhibit 2 is a short-acting bronchodilator (i.e., a bronchodilator drug such as terbutaline) with an immediate, short-term effect that may be used separately from the Symbicort® combination to quickly relieve asthma attacks as they occur. See, e.g., the paragraph of Exhibit 2 immediately below sentence "E", which says, "**There are no data available on the use of Symbicort Turbuhaler in the treatment of an acute asthma attack. Patients should be advised to have their rescue medication available at all times. Therapy [i.e., with Symbicort Turbuhaler] should not be initiated during an exacerbation.**" This shows that Exhibit 2 did not consider Symbicort® to be useful for treatment of an acute asthma attack nor to alleviate an ongoing exacerbation. Instead, the patient is advised to keep a separate "rescue medication" (i.e., short-acting bronchodilator) available to relieve acute attacks on an emergency basis. According to sentence "E", an increased use of that rescue bronchodilator is an indication that the patient's underlying condition is worsening rather than improving as it should when on regular (i.e., twice daily) Symbicort® therapy. If the patient's condition is worsening when on Symbicort® therapy, the physician is told that reassessment of the therapy is warranted. Nowhere does Exhibit 2 suggest that the patient should ever try Symbicort® to relieve an acute attack. Nor does Exhibit 2 suggest that the patient should feel free to increase the number of times per day that Symbicort® is inhaled if his/her condition is worsening. In fact, Exhibit 2 makes it clear that neither of those strategies is something that should ever be done. Thus, Exhibit 2 directly contradicts the Examiner's assumptions about what would have been "obvious" to do. Physicians of skill in the art understood even in 2001 (i.e., long after the priority date) that the patient should be told to use his/her short-acting bronchodilator if the patient felt an acute attack coming on, and should be told not to try taking an extra dose of Symbicort®. Applicants submit that Exhibit 2 is strongly supports the

nonobviousness of the present claims in that it provides concrete, objective evidence of how those of skill in the art would have interpreted Carling's disclosure regarding how to administer a budesonide/formoterol combination.

The language quoted above from the Office action ends with the curious assertion, "**Further, if the patient did not need the additional administration, the prior art clearly reads on the claimed invention**." Applicants assume that by the term "the prior art," the Examiner is referring to Carling. If the Examiner is alleging that Carling "reads on the claimed invention," i.e., anticipates the claims, that should be explicitly laid out in a proper rejection under 35 USC § 102, with a showing as to how every limitation of each supposedly anticipated claim can be found in the reference, so that Applicants can respond appropriately. If instead the Examiner is saying that Carling discloses the claimed invention except for some limitation about a "need" for an "additional administration," Applicants point out that this is not an accurate assessment of either Carling or what the claims actually say. Independent claim 13 requires, *inter alia*, that the patient be administered "one or more additional doses on an irregular basis, wherein the one or more additional doses are administered as-needed, as determined by the patient." Claim 13 thus explicitly requires that the patient have actually received at least one "additional dose," and also that the "additional dose" have been administered as-needed, as determined by the patient. If throughout the course of treatment, some patient were given only a twice-per-day maintenance dose, and did not ever need or receive any of the "one or more additional doses" specified in claim 13, then that patient's treatment would not meet all of the criteria of claim 13. Similarly, independent claim 36 requires that the patient be administered both (i) a maintenance dose twice per day, and (ii) one or more additional doses on an irregular basis, when the patient expects to encounter an asthma inducing condition. If a given patient never took even one of those additional doses (e.g., because the patient went through the entire course of treatment without expecting to encounter an asthma inducing condition, or because the patient chose not to take any additional dose even when expecting to encounter such a condition), then that patient's treatment would not fall into claim 36. The remaining independent claims all similarly require, *inter alia*, administration of one or more doses on an irregular basis. Thus, they do not cover a method of treatment disclosed by Carling, who teaches only regular, twice-daily administration.

The Office action at page 14 mentions the Exhibit 3 that was attached to the 7/27/07 Reply, but only to dismiss (yet again) this Exhibit on the ground that it concerns an admixture of two drugs different from those recited in the present claims. Exhibit 3 was discussed in detail in the 7/27/07 Reply at pages 19-20, to which Applicants again refer the Examiner. Applicants have pointed out repeatedly in this prosecution that Exhibit 3 was submitted to provide additional evidence, consistent with and supportive of Exhibits 1 and 2, showing how those of ordinary skill in the art generally understood that an inhaled steroid-containing composition should be administered in the treatment of asthma. While not as directly on point as Exhibits 1 and 2, both of which concern budesonide-containing compositions, Exhibit 3 is consistent with them and provides further support to Applicants' position (and contrary to the Examiner's position) regarding how those of ordinary skill in the art would have interpreted Carling's disclosures. The Examiner has provided no explanation as to why she views as irrelevant this evidence of how the art understood that steroid-containing compositions other than budesonide should be administered. Applicants believe that the evidence in Exhibit 3, when taken with Exhibits 1 and 2, is dispositive of the question of how the art understood that inhalable steroid-containing compositions in general (and budesonide-containing compositions in particular) should be administered to treat asthma. Significantly, the Examiner has provided no evidence to contradict Applicants' evidence in this regard.

The Office action on pages 14-15 discusses Exhibits 4 and 5 that were filed with the 7/27/07 Reply. These two Exhibits were discussed in detail in the 7/27/07 Reply at pages 21-22 and 26-28. Rather than repeat it here, Applicants urge the Examiner to review that discussion. Briefly, Exhibit 4 (the O'Byrne et al. article) provides evidence of the surprising results produced by the presently claimed methods, results that are predicted nowhere in Carling. Exhibit 5 (the Barnes editorial) comments on the O'Byrne et al. results and supplies evidence that there was a long felt, unsatisfied need in the art for a method that accomplishes what O'Byrne et al. showed the present methods accomplish. The Barnes editorial also describes what amounts to past skepticism of experts regarding the claimed method, noting the previous concern that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid (thus showing that the art did not share the Examiner's belief that eight doses of 200 μg budesonide each can be "safely inhaled" by all

patients every day). Finally, the Barnes editorial characterizes the O'Byrne et al. findings as "remarkable" and "surprisingly good results," fully validating Applicants' contentions in that regard.

Despite this ample evidence of surprising results, the Examiner "does not find that the evidence overcomes the prior art for the reasons stated above." Office action at page 14. The Office action cites Carling's teachings about "greater efficiency and duration of bronchodilator action, and rapid onset action," but fails to note that this refers to the twice-daily administration taught by Carling (i.e., the only method taught by Carling), and not a method as presently claimed. The O'Byrne et al. study reported in Exhibit 4 compared the Carling twice-daily administration method to the presently claimed twice-daily-maintenance-plus-on-demand method, and found surprisingly better results with the latter. For example, O'Byrne et al. showed that only 16% of the patients who used the presently claimed method experienced severe exacerbations during the study, compared to 27% of the patients who used the Carling method (plus terbutaline for rescue purposes). O'Byrne et al. describes similarly striking benefits of the presently claimed method compared to the Carling method, using many other measures of efficacy (see the Results section on page 130, Figures 1 and 2, and Table 2 of O'Byrne et al.). None of this could have been predicted in view of Carling. Just because Carling said that the method disclosed in Carling had advantages over what had come before it gives no reason to expect that a method in accordance with the present claims would provide additional benefits, compared to Carling's method. If the Examiner intends to maintain the rejection over Carling, she is asked to address in particular her rationale for dismissing the significance of the O'Byrne et al. (Exhibit 4) evidence. Applicants would also appreciate having the Examiner's thoughts about the statements in the Barnes editorial (Exhibit 5) discussed above regarding surprising results; long-felt, unsatisfied need; and skepticism of experts. As the Examiner is no doubt aware, these are all important, objective indicia of nonobviousness that the courts have said must be taken into account when assessing obviousness.

Applicants wish to address some rather troubling assertions made on page 15 of the Office action. According to the Office action,

> The combination of Carling et al. provides suitable daily doses for asthma, but does not completely eliminate a patient taking more than two administrations a day.... Again, just

> because the combination is recommended to be taken twice daily does not mean that changes could not be made to accommodate the patient. Thus, the prior art reads on the patient taking an additional as-needed administration of the combination treatment. (Emphasis in the original.)

Applicants remind the Examiner that the question to be asked when determining whether a given claim is *prima facie* obvious is not whether the prior art "completely eliminates" the possibility of all steps of the claimed method being carried out. Nor is the appropriate standard based on whether "changes could not be made" to what the prior art actually discloses. If either of those were the standard, then every obviousness rejection would force the applicant into the position of having to prove that the claimed invention was impossible in view of the prior art's teachings. Virtually all inventions would be "obvious" under such a standard.

The proper standard to be applied in any obviousness situation is whether the prior art provides a reason to modify the art's teachings in order to arrive at the claimed method, and also provides an expectation that the modification will produce a successful result. In other words, the question to be asked is not whether one could have produced the claimed invention, but rather whether one would have done so. Even if Carling did not "completely eliminate" the possibility a patient could take more than two administrations a day, he certainly did not provide any reason that it should be done (much less a reasonable expectation that it would be successful). Accordingly, Carling does not make the claimed methods *prima facie* obvious.

For all the reasons stated above, withdrawal of the rejections over Carling is respectfully requested.

Rejection under 35 USC § 103(a) for Obviousness over Carling in view of Aberg and Ryrfeldt

Claims 16 and 19 remain rejected over Carling in view of Aberg et al., US Patent No. 5,795,564 (Aberg) and in further view of Ryrfeldt et al., Biochemical Pharmacology, 1989, 38(1), pages 17-22 (Ryrfeldt). The rejections over these references are set forth at pages 10-11 of the Office action. Claims 16 and 19 depend from claim 13, further limiting the formoterol to the R,R enantiomer of formoterol (claim 16) and the budesonide to the 22R epimer of budesonide (claim 19). Carling is cited as described above. Aberg is cited for its teaching of the (R,R) isomer of formoterol, as required by claim 16. Ryrfeldt is cited for its teaching of the 22R

epimer of budesonide, as required by claim 19. As established above, claim 13 is not obvious in view of Carling. Neither Aberg nor Ryrfeldt supplies what is missing from Carling with respect to claim 13. Accordingly, dependent claims 16 and 19, like the rest of the claims pending in the application, are not obvious over the cited art.

Withdrawal of the rejections for obviousness and allowance of the claims are respectfully requested.

The fee of $1,110.00 for the three-month extension of time is being filed herewith. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No: 06275-0188002.

Respectfully submitted,

Date: December 11, 2009

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